Journal of the Formosan Medical Association (2014) 113, 862—866

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.jfma-online.com

CASE REPORT

Hashimoto's encephalopathy: Report of three cases

Jan-Shun Chang [a], Tien-Chun Chang [a,b,*]

[a] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[b] Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

Received 9 December 2010; received in revised form 17 May 2011; accepted 18 May 2011

KEYWORDS
autoimmune thyroiditis;
encephalopathy;
hallucinations;
Hashimoto's thyroiditis;
steroids

Both severe thyrotoxicosis and hypothyroidism may affect brain function and cause a change in consciousness, as seen with a thyroid storm or myxedema coma. However, encephalopathy may also develop in patients with autoimmune thyroid diseases independent of actual thyroid function level, and this is known as Hashimoto's encephalopathy. Although most patients are found to have Hashimoto's thyroiditis, less frequently they have Graves' disease. Clinical manifestations include epilepsy, disturbance of consciousness, cognitive impairment, memory loss, myoclonus, hallucinations, stroke-like episodes, tremor, involuntary movements, language impairment, and gait impairment. Hashimoto's encephalopathy is a relatively rare disease. As a good response can be obtained with corticosteroid therapy, early diagnosis and treatment is very beneficial for patients. Here we report three patients with Hashimoto's encephalopathy with typical manifestations of hallucinations that were associated with hypothyroidism, hyperthyroidism, and euthyroid status, respectively. They all showed a dramatic response to methylprednisolone pulse therapy.

Introduction

Both severe thyrotoxicosis and hypothyroidism may affect brain function. Some encephalopathies that develop in patients with autoimmune thyroiditis are, however, independent of actual thyroid function level, and these are known as Hashimoto's encephalopathy. The first case was reported by Brain et al. in 1966,[1] and so far only about 200 cases have been reported, in adults as well as children.[2]

Schizophrenia is associated with genetic and environmental factors, and changes in neurotransmitter levels. The clinical picture consists of delusions, hallucinations, disorganized thinking, loss of social skills, stiffness, and other neuropsychiatric symptoms. However, some physical illnesses, such as electrolyte imbalance, hypoglycemia, central nervous system infections, thyroid and parathyroid diseases, liver and kidney failure, systemic lupus erythematosus, seizures, and neoplasms may induce similar psychotic symptoms.[3]

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.
E-mail address: tienchunchang@ntu.edu.tw (T.-C. Chang).

0929-6646/$ - see front matter
doi:10.1016/j.jfma.2011.05.012

Therefore, for all patients with unexplained acute or subacute encephalopathy, or atypical psychiatric manifestations, especially patients who have autoimmune thyroid disease, Hashimoto's encephalopathy must be included in the differential diagnosis. Here we present three cases of Hashimoto's encephalopathy associated with hypothyroidism, hyperthyroidism, and euthyroid status, respectively.

Case reports

Case 1

This patient was a 46-year-old man, who was relatively well, with no long-term medications or substance abuse history. He worked as a community security guard, and was responsible and friendly to the community residents and his co-workers. About 6 months before admission, he had presented with depressed mood, bilateral lower leg weakness, and inability to concentrate. Furthermore, his younger brother noticed self-talking behavior, paranoid ideas, and intermittent crying. Therefore, the man was brought to our hospital for admission.

On admission, physical evaluation disclosed clear consciousness but slow responses, a low-pitched voice, coarse hair, a moderately diffuse goiter, low body temperature (35.4°C), hand tremor, and myoclonus. Vivid visual hallucinations, auditory hallucinations, and paranoid ideas were also noted. Laboratory evaluation showed a free thyroxine (T_4) level <3.48 pmol/L, high-sensitivity thyroid stimulating hormone hsTSH) of 159.7 mIU/L, an antithyroid peroxidase (anti-TPO) antibody value of 1697.78 IU/mL, antithyroglobulin antibody (ATA) level of 154.07 IU/mL, creatine kinase of 14.4 μkat/L, and total cholesterol of 4.69 mmol/L (Table 1).

Thyroid echography showed a diffuse isoechoic and heterogeneous picture, which was compatible with autoimmune thyroiditis. Levothyroxine was prescribed for Hashimoto's thyroiditis with hypothyroidism. Magnetic resonance imaging (MRI) of the brain disclosed only mild prominent and symmetrical sulci, fissures, and ventricles. Electroencephalography (EEG) showed mild diffuse cortical dysfunction. The cerebrospinal fluid (CSF) had a slightly increased protein concentration (0.78 g/L), increased immunoglobulin G (IgG) level (0.18 g/L), a raised albumin concentration with a higher CSF:serum IgG ratio (0.007) and albumin ratio (0.01162), but no pleocytosis. In addition, positive ATA (2.03 IU/mL) and anti-TPO antibody (11.55 IU/ml) were also noted (Table 2).

Intravenous infusion therapy with methylprednisolone 500 mg in 200 mL normal saline for 30 minutes on three consecutive days rapidly improved the clinical picture. The visual hallucinations, auditory hallucinations, and paranoid ideas also totally recovered. Loss of short-term memory was noted. A subsequent EEG study 2 weeks later was normal.

The patient has now been symptom-free for 8 months without any recurrences, and has been followed up in the outpatient department to monitor his levothyroxine supplemental therapy. He has been able to work and maintain independent daily living during the follow-up period.

Case 2

The second patient was a 56-year-old woman known to be affected by Graves' disease with Graves' orbitopathy diagnosed when she was 43 years old by a moderate diffuse goiter and initial laboratory data revealing free T_4 of 28.32 pmol/L, hsTSH of 0.06 mIU/L, antimicrosomal antibody 1:20480 (+), and ATA 1:20480 (+). Thyroid echography showed a homogeneous diffusely isoechoic picture, which was compatible with Graves' disease. After taking methylprednisolone pulse therapy for active Graves' orbitopathy, the patient was treated with antithyroid drugs. Antithyroid drugs were discontinued after a total of 9 years' treatment when she was in a euthyroid state.

About 2 months after discontinuing her antithyroid drugs, the patient presented with disturbance of consciousness, gait disturbance, bilateral tremor of the hands, and delirium. Physical evaluation disclosed a body temperature of 36.2°C and sinus tachycardia (heart rate 110 beats per minute). Laboratory data showed a free T_4 value of 45.05 pmol/L and hsTSH <0.004 mIU/L. Brain MRI revealed non-specific findings, and EEG recording showed moderate diffuse cortical dysfunction. Suspecting a thyroid storm, high-dose propylthiouracil, beta-blockers, diluted Lugol's solution, and corticosteroid were prescribed, with a favorable response.

However, disturbance of consciousness, unstable gait, and visual hallucinations occurred 1 month later when the dose of steroid was tapered off. Physical examination

Table 1 Serum levels of free thyroid hormones, thyrotropin, and thyroid autoantibodies observed in the three patients with Hashimoto's encephalopathy described in the text.

	Case 1	Case 2	Case 3	Reference range
Hormones				
fT4 (pmol/L)	<3.48	25.87	13.51	7.72–22.52
hsTSH (mIU/L)	159.7	<0.004	0.64	0.1–4.0
Autoantibodies				
Anti-TPO (IU/mL)	1697.78			<5.61
AMA		1:20480 (+)	1:1280(+)	<1:80 (−)
ATA (IU/mL)	154.07	1:20480 (+)	1:5120(+)	<14.4
				<1:80 (−)

ATA = anti-thyroglobulin antibodies; AMA = antimicrosomal antibody, presented as titers; anti-TPO = anti-thyroid peroxidase antibodies; fT4 = free thyroxine; hsTSH = high sensitive thyroid-stimulating hormone; + means positive finding, and elevation of antibody titer; − means negative and normal.

Table 2 Cerebrospinal fluid (CSF) data in a 46-year-old man affected by Hashimoto's encephalopathy (Case 1).

Parameters	Values	Reference values
Appearance	Clear, colourless	—
Glucose (mmol/L)	3.16	2.78—4.16
Proteins (g/L)	0.78	<0.5
Albumin (g/L)	0.49	0.1—0.35
IgG (g/L)	0.18	<0.04
Oligoclonal IgG band	Absent	Absent
CSF:serum IgG ratio	0.007	<0.003
CSF:serum albumin ratio	0.01162	<0.009
Anti-TPO antibody (IU/mL)	11.55	Negative
ATA (IU/mL)	2.03	Negative
Erythrocytes	0	Absent
Leucocytes (n/mm^3)	0	<5
Lymphocytes (n/%)	0	40—80
Stain for microorganisms, including acid-fast bacteria, and antibodies for infectious pathogens	Negative	Negative

ATA = anti-thyroglobulin antibodies; anti-TPO = anti-thyroid peroxidase antibodies; IgG = immunoglobulin G.

showed a moderate diffuse goiter, a normal heart beat, and no fever (body temperature 36.8 °C). Laboratory evaluation disclosed free T_4 25.87 pmol/L and hsTSH <0.004 mIU/L (see Table 1). A diagnosis of Hashimoto's encephalopathy was suspected as the changes in thyroid hormone status could not justify the patient's symptoms.

She was treated with intravenous methylprednisolone 500 mg daily for 3 days, which resulted in a dramatic improvement. Loss of recent memory, especially relating to before admission, was also noted. Oral prednisone was prescribed and slowly tapered off within 9 months. The patient did not show any neuropsychiatric alterations even after corticosteroids had been discontinued. She was symptom-free for 5 years and was maintained in euthyroid state with low-dose propylthiouracil treatment for Graves' disease.

Case 3

A 76-year-old woman suffering from Hashimoto's thyroiditis was under regular medical control for hypertension. She had developed psychotic symptoms in the form of auditory hallucinations and persecutory delusions when she was 70 years old, and was then treated with low-dose risperidone treatment.

After about 3 years of stable treatment, there was a flare-up of her psychotic symptoms with disturbing behavior. Her consciousness was clear, but she suffered severe persecutory delusions and auditory hallucinations, and a moderate diffuse goiter was noted. Laboratory evaluation showed free T_4 13.51 pmol/L, hsTSH 0.64 mIU/L, antimicrosomal antibody 1:1280 (+), and ATA 1:5120 (+) (see Table 1). An EEG showed intermittent slow waves in both temporal areas, and MRI of the brain revealed nonspecific findings.

As this prompted a suspicion of Hashimoto's encephalopathy, methylprednisolone 500 mg intravenous pulse therapy was given for 3 days, with a rapid improvement in the patient's delusions. She received repeated steroid pulse therapies 1 and 6 months after first dose of methylprednisolone pulse therapy due to a flare-up of her psychotic symptoms, with a favorable response in both instances. Follow-up laboratory data showed decreased antimicrosomal antibody (1:1280 +) and ATA (1:640 +) titers, and the EEG was normal. The patient was regularly followed up in the outpatient department for 3 years, her psychotic symptoms remaining stable with low-dose antipsychotic agents.

Discussion

Hashimoto's encephalopathy is a rare disease, with a prevalence of 2.1/100,000.[4] As with other autoimmune thyroid diseases, Hashimoto's encephalopathy occurs predominantly in females, with a male to female ratio of approximately 1:5, and the mean age of onset is between 45 and 55 years.[5] Most patients with Hashimoto's encephalopathy are affected by Hashimoto's thyroiditis, although a small number have Graves' disease. The clinical features do not differ between patients with Hashimoto's thyroiditis or Graves' disease.[6]

The pathogenesis of Hashimoto's encephalopathy is still unknown. There is no evidence that the anti-TPO antibody directly causes encephalopathy, but other autoantibodies that associated with autoimmune thyroid diseases might induce encephalopathy. Some autopsy reports have noted that Hashimoto's encephalopathy may be associated with lymphocytic infiltration and vasculitis in the brainstem or brain gray matter.[7] Several mechanisms, such as autoimmune vasculitis, autoantibodies against brain-thyroid antigens, encephalomyelitis-associated demyelination, global cerebral hypoperfusion, a direct toxic effect of thyrotropin-releasing hormone, and neuronal dysfunction due to brain edema have been proposed for Hashimoto's encephalopathy.[8]

The condition is known by many names that refer to different pathophysiological mechanisms: (1) steroid-responsive encephalopathy associated with thyroid autoimmunity: with an emphasis on a good response to steroid therapy; (2) non-vasculitic autoimmune inflammatory meningoencephalitis, which covers many different etiologies; (3) Hashimoto's encephalopathy, as most patients have underlying Hashimoto's thyroiditis; and (4) encephalopathy associated with autoimmune thyroid disease, which contains a broad spectrum of conditions, not only Hashimoto's thyroiditis, but also Graves' disease.[9]

Hashimoto's encephalopathy is characterized by numerous neurological and neuropsychiatric symptoms. The clinical manifestations include epilepsy and disturbance of consciousness (51%), cognitive impairment and memory loss (48%), myoclonus (32%), hallucinations and psychotic symptoms (26%), stroke-like symptoms (21%), tremor and involuntary movements (12%), language barrier (8%), and ataxia (6%).[10] In children, the prevalence is still higher in girls than boys. The most common symptoms are seizures, altered consciousness, headache, and hallucinations.

The thyroid function of patients with Hashimoto's encephalopathy may manifest as subclinical hypothyroidism (35%), euthyroidism (30%), overt hypothyroidism (20%), or, less frequently, hyperthyroidism (7%).[11] It is different from myxedema coma or thyroid storm because the change in consciousness that occurs in Hashimoto's encephalopathy is unrelated to the level of thyroid hormone. As in our Case 2, although the thyroid hormone level was elevated, patient kept afebrile while consciousness disturbance developed. Because thyroid storm could not be completely ruled out in that case, the patient was initially treated for this. Psychotic symptoms recurred while the steroid dosage was being tapered off, and the changes in thyroid hormone were unable to justify the symptoms. Thus, a diagnosis of Hashimoto's encephalopathy was a high probability. After steroid pulse therapy with a good response, the diagnosis was confirmed.

According to the literature, psychosis may develop under steroid therapy, and the symptoms will improve after tapering the steroid off.[12] Steroid withdrawal syndrome is much more likely to be associated with symptoms of fever, anorexia, nausea, lethargy, and arthralgias, which resembles those of adrenal insufficiency.[13] In the second case we described here, the symptoms do not match the above criteria.

After excluding other possible etiologies of encephalopathy, Hashimoto's encephalopathy must be suspected in all patients with autoimmune thyroid disease who develop unexplained acute or subacute encephalopathy. The diagnostic criteria for Hashimoto's encephalopathy include: (1) a lack of other diseases such as infection, stroke, metabolic diseases, and other factors accounting for the acute or subacute encephalopathy; (2) euthyroidism or thyroid hormone changes that are unable to justify the symptoms; (3) an association with autoimmune thyroid diseases with an elevated plasma anti-TPO antibody level; and (4) a favorable response to corticosteroid therapy. If the patient's condition meets the above criteria, Hashimoto's encephalopathy can be diagnosed.[14]

As in our first case, additional clues may be provided by the detection of anti-TPO antibody and ATA, and an increase in protein concentration or IgG level in the CSF without pleocytosis.[15] Computed tomography scans, MRI of the brain and EEG traces are either normal or present with nonspecific findings. The role of imaging studies is mainly to exclude other possible causes of encephalopathy.

The literature reports that alpha-enolase and a 36-kDa protein, detected in a soluble fraction from the cerebral cortex, may play a role in Hashimoto's encephalopathy.[16,17] A further study suggests that autoantibodies are directed against the amino-terminal portion of alpha-enolase.[18] Thus, the detection of anti-alpha-enolase antibodies could be a possible additional tool in diagnosis. Elevated CSF protein levels during exacerbations that normalize during remission are reported.[11] The EEG also showed normalization after treatment; however, this occurs approximately 2 weeks later than the clinical improvement.[19]

Treatment for Hashimoto's encephalopathy is divided into three categories. The first approach is to use immunomodulatory agents. When Hashimoto's encephalopathy is suspected, corticosteroid treatment is advised as the first-line therapeutic choice. Various regimens of corticosteroid treatment have been proposed. According to the literature, methylprednisolone 1000 mg as an intravenous infusion for 3—5 days is recommended.[20] In Chinese patients, as shown by our experience in the three cases described above, the recommended dose can be reduced to methylprednisolone 500 mg intravenous infusion for 3 days to decrease the incidence of iatrogenic Cushing's syndrome and the risk for osteoporosis. The neurological symptoms usually respond within 1 week, sometimes as quickly as 1 day. In up to 40% of patients, there is no recurrence after the first course of corticosteroid pulse therapy.[9]

Occasional steroid resistance and a recurrence of psychiatric symptoms may occur. For patients with a recurrence of symptoms, the effectiveness of corticosteroid therapy remains good. Combination of oral prednisone (1 mg/kg/day) after high-dose corticosteroid can be considered for patients showing frequent recurrence, followed by progressive tapering until the drug is withdrawn after 6—12 months, depending on clinical evolution and responsiveness.[10,21] In patients with a poor response to corticosteroids, combination with azathioprine, cyclophosphamide, plaquenil, methotrexate, intravenous immunoglobulin (IVIG), or plasmapheresis has been reported.[11,22,23]

The second approach is to give thyroxine or an antithyroid drug, as it is beneficial to maintain a euthyroid status for patients with Hashimoto's encephalopathy. Third, treatment should be given for other complications: if a seizure occurs, antiepileptic drugs are considered, and if cerebral edema is predominant, infusion of mannitol may also be of benefit to reduce intracranial pressure.

In conclusion, Hashimoto's encephalopathy is an encephalopathy related to autoimmune thyroid diseases. Although the laboratory findings are nonspecific except to prove that the patient has autoimmune thyroid disease, and the imaging findings are used only to exclude specific lesions, early diagnosis and treatment is important as the response to steroid therapy is good. From our experience with Chinese patients, the dose of corticosteroid pulse therapy can be lower than that previously suggested in the literature, with the same dramatic effect.

References

1. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. *Lancet* 1966;**2**:512—4.
2. Payer J, Petrovic T, Baqi L, Lisy L, Langer P. Hashimoto's encephalopathy and rare cases of hyperthyroidism (review and case report). *Endocr Regul* 2009;**43**:169—78.
3. Patkar AA, Mago R, Masand PS. Psychotic symptoms in patients with medical disorders. *Curr Psychiatry Rep* 2004;**6**:216—24.
4. Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. *J Neurol Sci* 2004;**217**:165—8.
5. Mocellin R, Walterfang M, Velakoulis D. Hashimoto's encephalopathy: epidemiology, pathogenesis and management. *CNS Drugs* 2007;**21**:799—811.
6. Tamagno G, Celik Y, Simó R, Dihné M, Kimura K, Gelosa G, et al. Encephalopathy associated with autoimmune thyroid disease in patients with Graves' disease: clinical manifestations, follow-up, and outcomes. *BMC Neurol* 2010;**10**:27.
7. Nolte KW, Unbehaun A, Sieker H, Tm Kloss, Paulus W. Hashimoto encephalopathy: a brainstem vasculitis? *Neurology* 2000; **54**:769—70.

8. Schiess N, Pardo CA. Hashimoto's encephalopathy. *Ann N Y Acad Sci* 2008;**1142**:254—65.
9. Vernino S, Geschwind M, Boeve B. Autoimmune encephalopathies. *Neurologist* 2007;**13**:140—7.
10. Tamagno G, Federspil G, Murialdo G. Clinical and diagnostic aspects of encephalopathy associated with autoimmune thyroid disease (or Hashimoto's encephalopathy). *Intern Emerg Med* 2006;**1**:15—23.
11. Marshall GA, Doyle JJ. Long-term treatment of Hashimoto's encephalopathy. *J Neuropsychiatry Clin Neurosci* 2006;**18**: 14—20.
12. Sirois F. Steroid psychosis: a review. *Gen Hosp Psychiatry* 2003; **25**:27—33.
13. Margolin L, Cope DK, Bakst-Sisser R, Greenspan J. The steroid withdrawal syndrome: a review of the implications, etiology, and treatments. *J Pain Symptom Manage* 2007;**33**:224—8.
14. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? *Arch Neurol* 2003;**60**:164—71.
15. Ferracci F, Carnevale A. The neurological disorder associated with thyroid autoimmunity. *J Neurol* 2006;**253**:975—84.
16. Ochi H, Horiuchi I, Araki N, Toda T, Araki T, Sato K, et al. Proteomic analysis of human brain identifies alpha-enolase as a novel autoantigen in Hashimoto's encephalopathy. *FEBS Lett* 2002;**528**:197—202.
17. Oide T, Tokuda T, Yazaki M, Watarai M, Mitsuhashi S, Kaneko, et al. Anti-neuronal autoantibody in Hashimoto's encephalopathy: neuropathological, immunohistochemical, and biochemical analysis of two patients. *J Neurol Sci* 2004;**217**:7—12.
18. Fujii A, Yoneda M, Ito T, Yamamura O, Satomi S, Higa H, et al. Autoantibodies against the amino terminal of alpha-enolase are a useful diagnostic marker of Hashimoto's encephalopathy. *J Neuroimmunol* 2005;**162**:130—6.
19. Schäuble B, Castillo PR, Boeve BF, Westmoreland BF. EEG findings in steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Clin Neurophysiol* 2003;**114**:32—7.
20. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol* 2006;**63**:197—202.
21. Alink J, de Vries TW. Unexplained seizures, confusion or hallucinations: think Hashimoto encephalopathy. *Acta Paediatr* 2008;**97**:451—3.
22. Mijajlovic M, Mirkovic M, Dackovic J, Zidverc-Trajkovic J, Sternic N. Clinical manifestations, diagnostic criteria and therapy of Hashimoto's encephalopathy: report of two cases. *J Neurol Sci* 2010;**288**:194—6.
23. Hussain NS, Rumbaugh J, Kerr D, Nath A, Hillis AE. Effects of prednisone and plasma exchange on cognitive impairment in Hashimoto encephalopathy. *Neurology* 2005;**64**:165—6.